

Enol Esters. XII.¹ C-Acylation with Enol Esters

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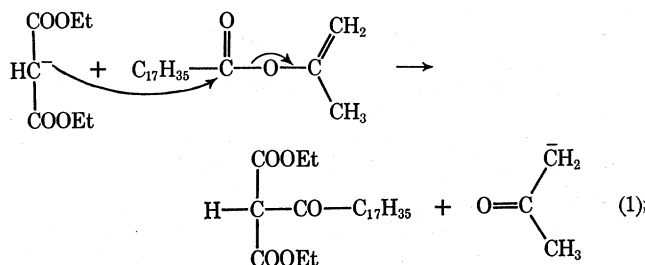
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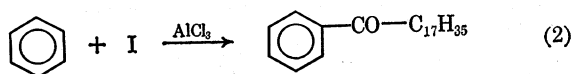
Isopropenyl esters under conditions of aluminum chloride catalysis provide a simple method of preparation of β -keto aldehydes and symmetrical β diketones. For example, isopropenyl stearate gives distearoylmethane. Under mild conditions vinyl stearate gives the β -keto aldehyde 3-oxoeicosanal, but on longer heating distearoylmethane results. With aromatic systems, isopropenyl stearate gives typical Friedel-Crafts acylation products in good yields. Palmitoyl chloride with aluminum chloride converts ethyl acetoacetate to ethyl palmitoacetate and ethyl dipalmitoacetate.

We have demonstrated in previous publications the usefulness of long-chain fatty acid enol ester derivatives in various types of chemical syntheses such as the acylation of OH, NH₂, RCONHR, Hal-H, SH, and SO₂NHR groups,^{3,4} and also the formation of cyclic derivatives from alkylketene self-condensations.⁵ In the present paper we wish to report the further utility of such enol esters (as exemplified by isopropenyl stearate and vinyl stearate) in carrying out acylations where in the acyl group becomes attached to carbon. As a result of our experiences with enol esters, we might summarize by stating that isopropenyl stearate (I), in general, resembles stearoyl chloride in its reactions but bears little chemical resemblance⁶ to its homolog, vinyl stearate. For example, isopropenyl esters are acylating agents whereas vinyl esters are not; compound I stearylates succinimide at 170° whereas the vinyl homolog is totally inert under identical conditions. We do, however, report here that under conditions of aluminum chloride catalysis both isopropenyl and vinyl esters behave alike to form diacylmethanes (*i.e.*, β diketones).

In studying C-acylations we allowed the anion of diethyl malonate to react with I and obtained the C-stearylated product shown in eq 1.



The versatility of I was further demonstrated by its ability to acylate benzene to form stearophenone in good yield in sharp contrast to saturated esters which do not⁷ ordinarily succeed in the Friedel-Crafts reaction (eq 2).



(1) For the previous paper in this series see E. S. Rothman, G. G. Moore, and A. N. Spec, *Tetrahedron Lett.*, 5205 (1969).

(2) Agricultural Research Service, U. S. Department of Agriculture.

(3) E. S. Rothman, S. Serota, and D. Swern, *J. Org. Chem.*, **29**, 646 (1964).

(4) E. S. Rothman, G. G. Moore, and S. Serota, *ibid.*, **34**, 2486 (1969).

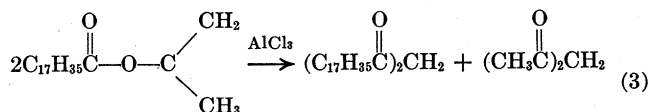
(5) E. S. Rothman, *J. Amer. Oil Chem. Soc.*, **45**, 189 (1968).

(6) E. S. Rothman, S. Serota, T. Perlstein, and D. Swern, *J. Org. Chem.*, **27**, 3123 (1962).

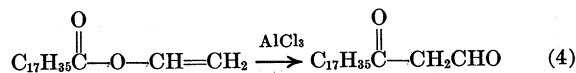
(7) P. H. Gore in "Friedel-Crafts and Related Reactions," Vol. III, Part I, G. A. Olah, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 34.

Aluminum chloride catalysis also enabled I to attack isolated olefinic bonds but gave low yields (35%) of α,β -unsaturated ketone. An interesting by-product, mp 77°, always accompanied the ketone, and, instead of pursuing the unsatisfactory olefinic ketone, we gave our attention to the crystalline by-product. The by-product was obtained from several different olefin acylation reactions so that we concluded that it arose solely from I. The compound showed unusual carbonyl absorption in the infrared in chloroform solution in the region where carbon disulfide is opaque. These bands are characteristic of β diketones, and elemental analysis, the nmr singlet at 5.58 ppm, strong ultraviolet absorption in isooctane at 274 m μ (E 10,000), together with the ability to form colored copper chelate complexes all led to the formulation of the side-reaction product as that of a diacylmethane.

By way of confirmation, it was found that solutions of isopropenyl esters in hexane in the absence of olefins on treatment with 0.25 to 1.0 mol of aluminum chloride also gave, after work-up with dilute acid, distearoylmethane⁸ in typically 75% yield, eq 3. In view of the



fact that vinyl esters, as mentioned before, usually take reaction paths different⁹ from those of the isopropenyl esters, we were interested to see what their behavior toward aluminum chloride would be. We found that the nature of the reaction product was strongly controlled by the length of reaction time. In a short reac-



tion time, the product obtained was the expected β -ketoaldehyde,⁹ eq 4; however, on somewhat longer re-

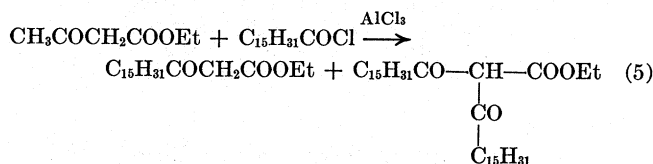
(8) Two preliminary communications have been submitted concerning β dicarbonyl compounds: (a) E. S. Rothman and G. G. Moore, *Tetrahedron Lett.*, 2553 (1969); (b) ref 1.

(9) The β -keto aldehydes are stable compounds in the protected copper chelate form, but after removal of the metal atom (with dilute acid) are sensitive to chromatography on silica gel and Florisil. An intense red coloration quickly develops and rechromatography leads to the isolation of three products: (a) white, mp 86-87°; (b) yellow, mp 72-72.7°; (c) red, unstable. The first two appear to be aldol and bisaldol products; the third shows aromatic bands in the nmr. These same products are encountered in the preparation of β -keto aldehydes by the published methods^{10a} involving the condensation of alkyl methyl ketones with ethyl formate using sodium metal catalyst.

(10) (a) V. Prelog, O. Metzler, and O. Jeger, *Helv. Chim. Acta*, **30**, 681 (1947); T. Kosuge, Japanese Patent 2171 (1954); *Chem. Abstr.*, **49**, P14800f, (1955). (b) Cf. A. Sieglitz and O. Horn, *Chem. Ber.*, **84**, 607 (1951).

fluxing, the product isolated was exclusively the same β diketone obtainable from the isopropenyl ester.

Under conditions of aluminum chloride catalysis we have obtained interesting reactions with acetoacetic ester-palmitoyl chloride mixture. The two products isolated are palmitoacetic ester and dipalmitoacetic ester, eq 5. The former forms a blue-green copper



chelate and the latter a lilac-colored copper chelate. In occasional runs small amounts of dipalmitoylmethane were detected, presumably arising from hydrolytic decarboxylation of dipalmitoacetic ester.

Since these data, in particular those giving vinyl ester product change with time, show that acyl interchange can occur, one is alerted to the possibility, among others,^{10b} that the formation of distearoylmethane from the aluminum chloride catalyzed reaction of isopropenyl stearate may occur *via* quasi-Fries rearrangement of isopropenyl stearate to form acetyl stearyl-methane as the proximate product which subsequently is converted to distearoylmethane.

Experimental Section

Diethyl 2-Stearoylmalonate.—To 8 g of diethyl malonate in 150 ml of toluene was added 1.15 g of finely divided sodium. After the sodium reacted, 16.2 g of isopropenyl stearate was added and the mixture refluxed for 2.5 hr. The cooled mixture was shaken with 4.5 ml of hydrochloric acid, the sodium chloride removed by filtration, and the toluene removed by evaporation *in vacuo*. The residue was dissolved in pentane, 1.3 g of stearic acid (insoluble) was removed by filtration, and the filtrate was chromatographed on a 45 × 4 cm silica gel column. Elution with pentane removed traces of toluene and unreacted isopropenyl stearate. Elution with 2–20% methylene chloride in pentane washed out 3.12 g of ethyl stearate. The product was eluted by 30–50% methylene chloride in pentane. (Further elution with methylene chloride removed an additional 1.4 g of stearic acid.) The product, recrystallized from ethanol, melted from 55.5 to 56.5°: *ir* 1758, 1721 to 1737 broad doublet cm^{-1} (CS_2); *uv* 245 μ (E 6550) (ethanol), 272 μ (E 18,800) (ethanol containing sodium hydroxide) (C-alkylation).

Anal. Calcd for $\text{C}_{25}\text{H}_{46}\text{O}_5$: C, 70.38; H, 10.89. Found: C, 70.60; H, 10.88.

Stearophenone from Isopropenyl Stearate.—Benzene (12 g, 0.15 mol), aluminum chloride (5.3 g, 0.04 formula wt), and isopropenyl stearate (6.48 g, 0.02 mol) were refluxed together for 10 min. The cooled mixture was poured onto iced dilute hydrochloric acid, and the ketone was isolated by extraction with ether. The residue, recrystallized from ether, gave 4.14 g (60%) of stearophenone, mp 62.5–63.5°, identical with an authentic sample.¹¹

4-Methylstearophenone.—To toluene (6.5 g, 0.079 mol) and aluminum chloride (3.3 g, 0.024 formula wt) was added 3.0 g (0.0093 mol) of isopropenyl stearate. After 5 min of reflux and work-up as described just above, 2.65 g (83%) of 4-methylstearophenone, mp 67–67.7° (lit.¹² mp 67°), was obtained.

2,4-Dimethylstearophenone.—*m*-Xylene (9.5 g, 0.090 mol), aluminum chloride (2.66 g, 0.02 formula wt), and 3.24 g of isopropenyl stearate (0.01 mol) were stirred together at 30° for 10 min, refluxed for 10 min, and worked up as the above examples. Recrystallization from ethanol gave 2.35 g (63%) of ketone, mp 45.5–46.5° (lit.¹³ mp 39°).

3,4-Dimethylstearophenone.—In like manner *o*-xylene gave a 66% yield of ketone: mp 51.0–51.5°, *ir* (CS_2) 685 cm^{-1} ($\text{C}=\text{O}$).

Anal. Calcd for $\text{C}_{26}\text{H}_{44}\text{O}$: C, 83.80; H, 11.90. Found: C, 83.96; H, 12.07.

8,10-Dioxoheptadecane (Dioctanoylmethane). Procedure A.—Isopropenyl octanoate, bp 65° (8 mm) (prepared by the sulfuric acid catalyzed exchange reaction between octanoic acid and isopropenyl acetate)⁶ (18.4 g, 0.1 mol), in 60 ml of olefin-free hexane, was heated with a total of 14.3 g (0.11 mol) of aluminum chloride delivered in three equal portions at 5-min intervals. The mildly exothermic reaction mixture was cooled to maintain near room temperature. After 1 hr, the mixture was poured into dilute hydrochloric acid-methylene chloride mixture. The separated, washed, and dried (sodium sulfate) organic layer was evaporated to a small volume and chromatographed on Florisil to give a pale yellow oil freezing to a solid in the refrigerator. Recrystallization from pentane in the cold gave a 70% yield of colorless plates: mp 20–21°; *uv* 274 μ (E 11,000) (isooctane); *nmr* 5.58, 3.56 ppm.

Anal. Calcd for $\text{C}_{17}\text{H}_{32}\text{O}_2$: C, 76.06; H, 12.02; mol wt, 268.24022 g/mol. Found: C, 76.05; H, 11.92; mol wt, 268.24051 g/mol (CEC Model 21-110-B mass spectrophotometer).

Copper Chelate Derivative.—Hot solutions in ethanol of cupric acetate and the dione were combined and let cool to deposit pale blue fibrous needles, mp 108.2–109.5°. Recrystallization from ethanol gave the analytical sample: mp 110.2–110.7°; *ir* 1350 (w), 1410 (s), 1458 (w), 1554 (s) CHCl_3 .

Anal. Calcd for $\text{C}_{34}\text{H}_{62}\text{O}_4\text{Cu}$: C, 68.24; H, 10.44. Found: C, 68.27; H, 10.42.

18,20-Dioxoheptatriacontane (Distearoylmethane). Procedure B.—Isopropenyl stearate (19 g, 0.059 mol) in 25 ml of hexane, was treated with 8.5 g (0.06 mol) of aluminum chloride. After stirring at 40° for 0.5 hr the mixture was worked up as above (occasional emulsion problems were corrected by methanol). The product is exceedingly insoluble in methanol. Crystallization from hexane and from ether gave a 65% yield of the diketone: mp 77.3–77.8°, lit.¹⁴ mp 75–76°; *uv* 273 μ (E 12,000) (isooctane); *ir* 6.24 μ (CHCl_3); *nmr* 3.54, 5.41 ppm. When only 0.25 mol of aluminum chloride was used, the yield was 50%.

Anal. Calcd for $\text{C}_{37}\text{H}_{72}\text{O}_2$: C, 80.95; H, 13.22; mol wt, 548. Found: C, 80.93; H, 13.28; mol wt, 516 (thermistor, CHCl_3).

The dioxime melted at 92.5–93.5° (lit.¹⁴ mp 90–92°).

Copper Chelate Derivative.—Hot solutions of aqueous cupric chloride and of the β diketone in ethanol were mixed, the pH was adjusted to about 7 with potassium carbonate, and the solution was allowed to cool to deposit lilac crystals of the chelate. These, separated and recrystallized from benzene and from chloroform, melted at 113.2–114.3°.

Anal. Calcd for $\text{C}_{74}\text{H}_{142}\text{O}_4\text{Cu}$: C, 76.65; H, 12.35. Found: C, 76.99; H, 12.31.

16,18-Dioxotritriacontane (Dipalmitoylmethane).—In an analogous manner (procedure B), isopropenyl palmitate gave dipalmitoylmethane, mp 71.8–72.1°.

Anal. Calcd for $\text{C}_{33}\text{H}_{64}\text{O}_2$: C, 80.40; H, 13.11. Found: C, 80.33; H, 13.50.

The copper chelate had mp 113.2–114.3°, lilac color.

Anal. Calcd for $\text{C}_{66}\text{H}_{126}\text{O}_4\text{Cu}$: C, 75.67; H, 12.15. Found: C, 75.50; H, 12.00.

12,14-Dioxopentacosane (Dilauroylmethane).—Analogously, isopropenyl laurate gave dilauroylmethane, mp 53° (lit.¹⁵ mp 50°), copper chelate mp 110° (lit.¹⁶ mp 102–104°).

Reaction of Vinyl Alkanoate with Aluminum Chloride to Form β -Keto Aldehyde. Procedure C. **3-Oxoecosanal.**—Vinyl stearate (15.45 g, 0.05 mol) in 50 ml of olefin-free hexane was heated with 6.7 g (0.05) of anhydrous aluminum chloride added in one portion. The mixture was then brought to reflux temperature, held there for 20 min, cooled, and poured into methylene chloride-iced dilute hydrochloric acid mixture. The organic layer was separated, dried (sodium sulfate), and evaporated under nitrogen to give 10.5 g (68%) of a crystalline residue of crude keto aldehyde, mp 42–47°. Recrystallization from ethanol gave erratic results. The analytical sample, recrystallized from pentane, melted at 60–61°: *uv* 269 μ 269 μ (E 6000) (isooctane); *ir* 1630, 1590, 1459, 1087 (CHCl_3); *ir* 720, 769 (CS_2); *nmr* 5.45 ppm doublet ($J = 4.5$ Hz), 7.89 ppm doublet ($J = 4.5$ Hz) (enols).

(14) R. Toubiana, *C. R. Acad. Sci., Paris*, **248**, 247 (1959); R. Toubiana and J. Asselineau, *Ann. Chim. (Paris)*, **7**, 593 (1962).

(15) A. Sieglitz and O. Horn, *Chem. Ber.*, **84**, 607 (1951).

(16) B. Helferich and H. Koster, *ibid.*, **56**, 2090 (1923).

(11) F. L. Breusch and M. Oguzer, *Chem. Ber.*, **87**, 1225 (1954).

(12) F. Krafft, *ibid.*, **21**, 2268 (1888).

(13) A. Claus and H. Haefelin, *J. Prakt. Chem.*, [2] **54**, 391 (1896).

Anal. Calcd for $C_{20}H_{38}O_2$: C, 77.36; H, 12.34; mol wt, 310.5. Found: C, 76.60; H, 12.48; mol wt, 314 (thermistor).

Copper Chelate.—Hot aqueous cupric acetate and an ethanolic solution of the keto aldehyde were combined and cooled to deposit blue-green crystals of the chelate: mp 128–129°; uv 245 m μ (E 7300), 302 (8900); ir, 1585, 1498, 1445, 1350 cm^{-1} ($CHCl_3$).

Anal. Calcd for $C_{40}H_{74}O_4Cu$: C, 70.39; H, 10.93. Found: C, 70.53; H, 10.94.

Dechelation.—A solution of the chelate in warm chloroform was shaken with 0.1 *N* hydrochloric acid, and the chloroform layer was washed with water, dried (sodium sulfate), and evaporated to yield a residue of the free keto aldehyde identical in properties with the sample described above.

3-Oxooctadecanal.—By a method analogous to procedure C, vinyl palmitate was converted to the C-18 3-keto aldehyde: mp 51.5–52.2° (lit.¹⁰ mp 47°); ir and uv very like those of the C-20 compound; copper chelate, mp 125–126.5°.

3-Oxotetradecanal.—By a method analogous to procedure C, vinyl laurate was converted to the C-14 3-keto aldehyde: mp 32.5–33.0°; ir and uv very similar to those of the C-18 and C-20 homologs. The pure crystalline compound was not stable to storage.

The copper chelate had mp 126.8–127.4°.

Anal. Calcd for $C_{28}H_{50}O_4Cu$: C, 65.38; H, 9.82. Found: C, 65.38; H, 9.81.

Reaction of Vinyl Alkanoate with Aluminum Chloride to Form β Diketones. Procedure D. **18,20-Dioxoheptatriacontane (Distearoylmethane).**—Vinyl stearate (23.4 g, 0.075 mol) in 200 ml of olefin-free hexane was treated with 10.15 g (0.075 mol) of aluminum chloride, and the mixture was refluxed for 2 hr, cooled, quenched by agitation with dilute hydrochloric acid, and dried (sodium sulfate), and the solvent was removed *in vacuo*. The residue weighed 8.5 g and more material (10 g) was recovered from the aqueous acid by methylene chloride–ether extraction.

The residues were combined, dissolved in hot 95% ethanol, and treated with an excess of hot aqueous cupric acetate to deposit a 73% yield of the lilac chelate identical with the preparation described above. [Where mixtures of the keto aldehyde and diketone were obtained as, for example, in intermediate reaction times (compare procedures C and D), separation was effected by chromatography of the mixed chelates on Florisil. Elution with hot benzene gave a forerun of the lilac chelated distearoylmethane followed by the blue-green chelated 3-oxoeicosanal. Additional chelated keto aldehyde was eluted with chloroform.]

16,18-Dioxotritriacontane (Dipalmitoylmethane).—In a manner analogous to the above (procedure D) vinyl palmitate was converted to dipalmitoyl methane.

12,14-Dioxopentacosane (Dilauroylmethane).—In a manner analogous to the above, vinyl laurate was converted to dilauroylmethane.

Ethyl Palmitoacetate and Ethyl Dipalmitoacetate.—Acetoacetic ester (3.6 ml, 0.028 mol) and 7.62 g of palmitoyl chloride (0.028 mol) in 50 ml of olefin-free hexane were treated with 3.7 g (0.028 formula wt) of aluminum chloride added in one portion. The pasty mixture was warmed for 2 hr at 70° during which time all solids dissolved. The mixture was cooled, poured into iced dilute hydrochloric acid, and extracted into ether. A little ethanol was used to break emulsions. The organic layer was dried (sodium sulfate), solvents were removed, and the product was chromatographed on Florisil. The first pentane eluates contained 1 g of dipalmitoylacetate purified by recrystallization of the copper chelate from ethanol: mp 91.9–92.3°; uv 297 m μ (E 26,000), 241 (18,000).

Anal. Calcd for $C_{72}H_{134}O_8Cu$: C, 72.58; H, 11.34. Found: C, 72.88; H, 11.34.

Dechelation with hydrochloric acid gave the free dipalmitoylacetate, mp 42–43°, uv 280 m μ (E 92000) (EtOH). Further elution of the column with methylene chloride gave palmitoacetic ester which, after recrystallization from hexane, melted from 38.7 to 39.2°, copper chelate mp 112–114° (lit.¹⁶ mp 37–38 and 111°, respectively).

Registry No.—I, 6136-89-6; vinyl stearate, 111-63-7; diethyl 2-stearoylmalonate, 24514-82-7; 3,4-dimethylstearophenone, 24514-83-8; 8,10-dioxoheptadecane, 24514-84-9; copper chelate of 8,10-dioxoheptadecane, 24523-20-4; 18,20-dioxoheptatriacontane, 24514-85-0; copper chelate of 18,20-dioxoheptatriacontane, 24515-38-6; 16,18-dioxotritriacontane, 24514-86-1; copper chelate of 16,18-dioxotritriacontane, 24515-39-7; 3-oxoeicosanal, 24514-87-2; copper chelate of 3-oxoeicosanal, 24515-40-0; 3-oxotetradecanal, 24514-88-3; copper chelate of 3-oxotetradecanal, 24515-41-1; ethyl dipalmitoacetate, 24514-89-4; copper chelate of ethyl dipalmitoacetate, 24515-42-2.